Androgens and hair growth

☆ *Androgen-stimulated hair growth = androgen-dependent*

- facial, trunk and extremity hair in the **male**
- pubic and axillary hair in **both sexes**
- development of hair at these sites at **puberty** (rise in levels of androgens from **testicular, adrenocortical** and **ovarian** sources, which occurs in both sexes and is somewhat more obvious in males)

☆ *Androgenetic alopecia (AGA)*

- Testosterone (T) is converted into the more potent metabolite 5α-dihydrotestosterone (DHT) – catalysed by the enzyme 5α-reductase (two isoforms)
  - Type 1 5α-reductase is widely distributed in the skin
  - Type 2 isoform is restricted to androgen target tissues such as the prostate and the epididymis
- In genetically-susceptible persons, T and DHT convert terminal hair of the **vertex** into vellus hair (NB. **Occipital region is less sensitive**)

Hair disorders				
↓ Growth			↑ Growth	
Alopecias			Hirsutism	Hypertrichosis
Non-cicatricial (Non-permanent)		Cicatricial (Scarring)		
Thinning	Shedding	e.g. DLE	Females Androgen-dependent sites Terminal hair	Females & males Any site Any type
Androgenetic alopecia (AGA)	AE TE			

4

Hypertrichosis

Definition

Growth of excessive amount of hair (3)

- in BOTH **males and females**
- **any type of hair** (lanugo, vellus, or terminal)
- on **any area** of the body

DD: Hirsutism: excessive growth of hair

- only in **women**
- only **terminal** hairs
- in a **"male pattern" distribution** e.g. moustache, beard, … etc
- due to ***androgen overproduction*** or ***increased end-organ sensitivity to androgens***

Classification: Hypertrichosis can be classified according to

- **distribution** (generalized / localized)
- **age** of onset (congenital / acquired)
- **type** of hair (lanugo / vellus / terminal).

Hypertrichosis	
Generalized	**Localized**
Congenital: • *Congenital hypertrichosis lanuginosa* • *Congenital generalized hypertrichosis*	**Congenital:** • *Congenital localized hypertrichosis* • *Localized hypertrichosis in hereditar diseases*
Acquired: • *Acquired hypertrichosis lanuginosa* • *Acquired generalized hypertrichosis* • *Prepubertal hypertrichosis*	**Acquired:** • *Acquired localized hypertrichosis* • *Localized hypertrichosis in acquired systemic diseases*

Generalized hypertrichosis

The presence of lanugo hair, excess vellus or terminal hair on **much of th skin surface** (including acquired transformation of terminal → lanugo ha

• Congenital hypertrichosis lanuginosa

* **Rare – AD**
* **lanugo hair is not replaced** by normal vellus hair
* **fine, silvery-gray to blond hair** continues to grow (lengths of up to 1 cm) covering the **entire body surface except** for the palms, soles, dorsa surface of the distal phalanges, and prepuce → **"dog" or "monkey" fa**
* Associations: dental abnormalities, malformations of the ear, glaucom pyloric stenosis, photophobia, and, rarely, physical and mental retardati
* **Persistent – TR: laser hair removal** مهم جدا

- **Congenital generalized hypertrichosis**
  - rare inherited disorders may present with congenital generalized hypertrichosis (may be present at birth or early in life)
    - ☆ *as the sole manifestation* e. g.
      - **Universal hypertrichosis (AD)** → thicker, longer hair most prominent on the frontal, temporal and preauricular areas of the face, the back and the proximal extremities – Increases during infancy and tends to persist
      - **X-linked hypertrichosis (XLR)**
    - ☆ *in association with other features*
      - **Gingival fibromatosis with hypertrichosis (AD)**
      - Acromegaly + hypertrichosis
  - **Intrauterine exposure to medications** such as **minoxidil** can also lead to congenital generalized hypertrichosis

- **Acquired hypertrichosis lanuginose** مهم جدا
  - **Paraneoplastic** مهم جدا disease
  - Associated with a variety of **internal malignancies**, most often carcinoma of the lung, colon or breast.
  - may also be associated with **other paraneoplastic dermatoses** such as acanthosis nigricans, palmoplantar keratoderma, the sign of Leser Trélat and acquired ichthyosis
  - The lanugo hair appears over the **entire body within a short period** of time, although in **mild forms** it may be **localized to the face**, leading to a **"simian" appearance**.
  - Lanugo hair may even develop in areas of androgenetic alopecia.

Acquired generalized hypertrichosis

- **Drug-induced** hypertrichosis (**most common cause, iatrogenic**) مهم
  - e.g. **Minoxidil**, Phenytoin, **Cyclosporine** (systemic, topical), **Glucocorticosteroids** (systemic, topical, intra-lesional)
  - **Slow** growth (may take **months**) of **terminal** hairs
  - usually **reversible**
- A sign or complication of **systemic conditions**:
  - disorders of the CNS (e.g. traumatic brain injuries)
  - *POEMS syndrome* (*p*olyneuropathy *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy and *s*kin lesions)
  - Others: juvenile hypothyroidism, juvenile dermatomyositis, and advanced HIV infection.

- **Prepubertal hypertrichosis**
  - **common** finding in **otherwise healthy** infants and children
  - most common in individuals of *Mediterranean / South Asian* descent
  - Pigmented hair is present in a **widespread, diffuse** distribution
    - face (especially the forehead, temples and preauricular area)
    - bushy eyebrows and a low anterior hairline
    - proximal extremities
    - back → **"inverted fir tree"** pattern
  - becomes more obvious during **childhood**
  - there may be a **family history** of excessive hairiness
  - mildly elevated **serum levels of total and free testosterone** is observed in a subset of **girls** with prepubertal hypertrichosis, while others have a normal androgen profile
  - **multiple etiologies** for this clinical pattern of hypertrichosis (androgen excess + constitutional susceptibility for hair growth)

Localized hypertrichosis

- **Congenital localized hypertrichosis** أول 4 مهمين
  - **Congenital melanocytic nevi**
  - **Becker's nevus (Becker's melanosis)**
  - **Spinal dysraphism**
    - Spinal dysraphism = abnormal closure of the neural tube → defects in the vertebral column and/or spinal cord
    - Skin lesions "marking" a hidden vertebral defect are usually located in the dorsal midline
    - The **"faun tail" sign:** a sign of spina bifida occulta or split spinal cord - located in the lumbosacral region
  - **Hair collar sign**
    - a ring of hypertrichosis surrounding membranous aplasia cutis
  - **Plexiform neurofibromas**
  - **Hypertrichosis may overlie the following skin lesions:** plaque-type blue nevus, fibrous hamartoma of infancy, dermal dendrocyte hamartoma, eccrine angiomatous hamartoma, congenital plaque-like glomangioma, tufted angioma.
  - **Nevoid hypertrichosis:** uncommon growth of terminal hairs in localized area
    - *Primary nevoid hypertrichosis:*

      NO extra-cutaneous associations / the skin within the affected area is normally pigmented and there is **no underlying hamartoma**
    - *Secondary nevoid hypertrichosis:* May be associated with lipodystrophy, hemihypertrophy, scoliosis and abnormalities of the underlying vasculature. May occur **with** epidermal nevi or nevoid hypopigmentation **"twin spotting**

- **Localized hypertrichosis in hereditary diseases**

Genodermatoses characterized by the presence of localized hypertrichosis as a major or secondary diagnostic feature – For example:

- Hypertrichosis within sun-exposed areas in **porphyrias** (mainly porphyria cutanea tarda + congenital erythropoietic porphyria)
- **EB dystrophica**
- Hypertrichosis cubiti (hairy elbow syndrome)
- Hypertrichosis of the auricle
- Hypertrichosis of the eyebrows
- Trichomegaly of the eyelashes

- **Acquired localized hypertrichosis**

- After **repeated trauma, friction, irritation or inflammation**, the hair within affected areas of skin may become longer and thicker e.g.
  - hypertrichosis of the back in sack carriers
  - hypertrichosis of a fractured limb after the application of a plaster cast
  - hypertrichosis of the posterior neck in people who bear heavy weights
- Sites of **chronic rubbing and scratching** due to pruritus
- Transient localized hypertrichosis within **vaccination sites, varicella scars, sites of wart removal and laser epilation**
- Hypertrichosis overlying **lipoatrophy** following lupus panniculitis and within resolving lesions of psoriasis and morphea.
- after **PUVA therapy**
- at sites of **application of potent topical corticosteroids, tacrolimus, and creams containing mercury or iodine**
- sites of repeated **irritation from anthralin**
- **Prostaglandin F-2α analogues** مهم جداً (e.g. latanoprost, bimatoprost) – topical agents used for the treatment of glaucoma
  - induce trichomegaly of the eyelashes + brown iris pigmentation
  - **bimatoprost** is FDA-approved for the **enhancement of eyelash growth**
  - **Latanoprost** is used to treat **eyelash alopecia** in alopecia areata universalis

- **Localized hypertrichosis in acquired systemic diseases**
  - Infra-patellar hypertrichosis in juvenile dermatomyositis
  - hypertrichosis overlying pretibial myxedema, indurated plaques of Rosai–Dorfman disease, and areas affected by reflex sympathetic dystrophy.

NB. Most cases of localized hypertrichosis involve a switch from vellus to terminal hair in sites that do not usually bear terminal hair.

Treatment of hypertrichosis

Treatment of the **cause** (e.g. drug withdrawal) – [illegible]

- **Shaving** and other cosmetic maneuvers (e.g. plucking)
- **"depilation"** with **creams**
- **Electrolysis**
- hair removal with **lasers** "**epilation**": [illegible]
- hair removal using **intense pulsed non-coherent light source** (IPL)

QQ Compare: Depilation / Epilation

Medical Treatment For Male And Female Pattern Hair loss

By

DR. Ahmed Sadeq

Professor of Dermatology, Venereology and Andrology,
Al Azhar University

Nomenclature

- Common baldness , Androgenitic alopecia patterned or premature baldness.

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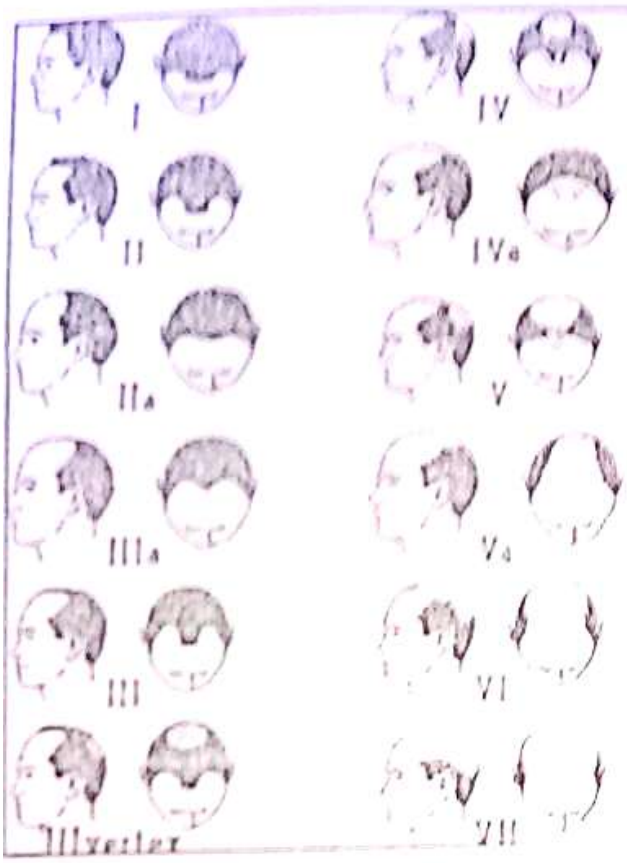
- **Hamilton** (1951) defined the pattern of male baldness and produced the first useful grading scale (1 – 7).
- **Norwood** (1975) added 2a, 3a, 3 vertex, 4a & 5a.



Norwood's classification of male balding

3

Male Characteristic Baldness

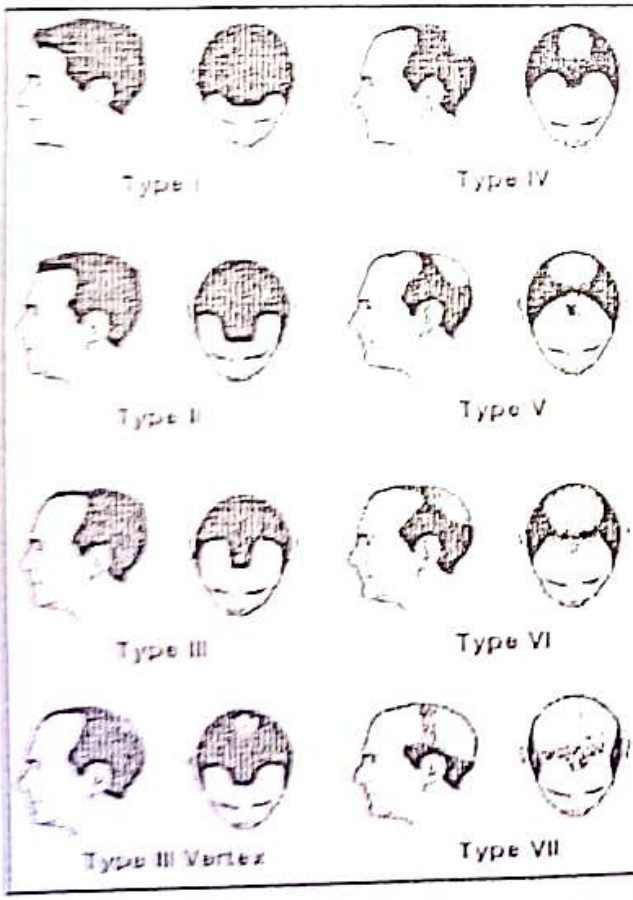
Scanned by CamScanner

male
Chamilton & Norwood

female
Ludwig

- **Ludwig** (1977) described the most common pattern of hair loss in women and it was used as grading scale (1-3).
- **Sinclair et al,** (2004) prescribed other validated useful scales.

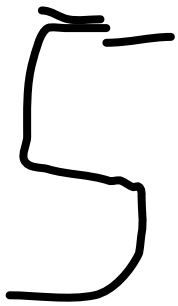
patterned or premature baldness.



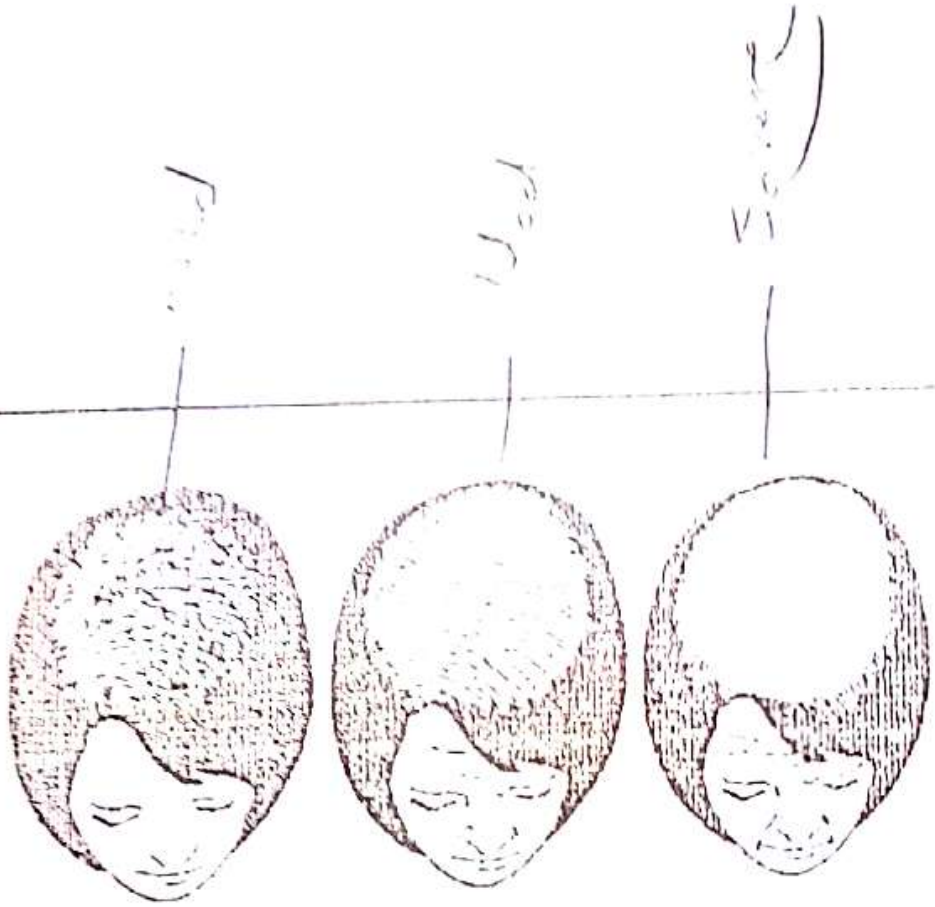
Hamilton scale

4

- The grades are useful as diagnostic aides & in the classification of extent of hair loss in clinical investigations.
- The pattern of hair loss and presentation of AGA in women differ from men.
- Women may present with episodic or contin increase in hair shedding without reduction of hair volume or both or only diffuse thinning over the crown.



in hair shedding without reduction of hair volume or both or only diffuse thinning over the crown.



Ludwig patterns of hair loss

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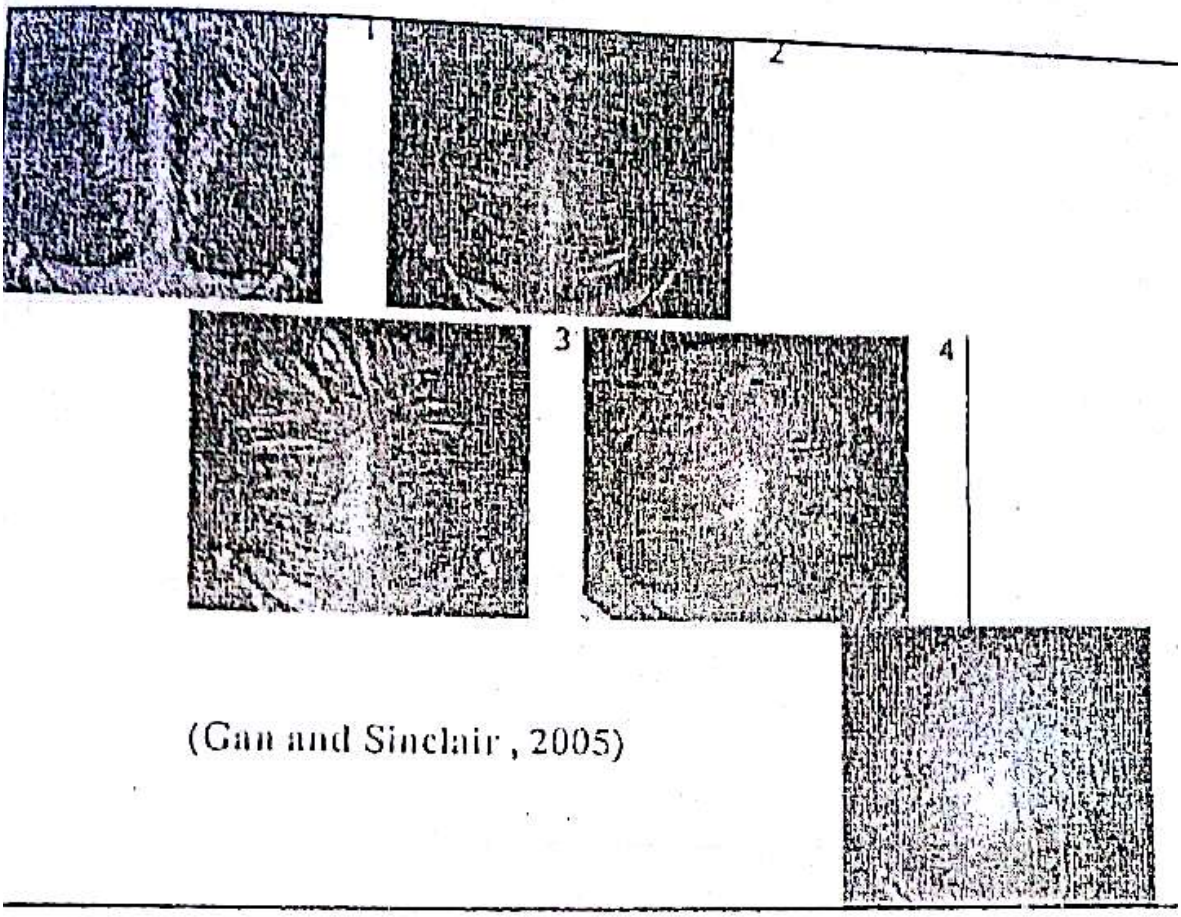

(Gan and Sinclair , 2005)

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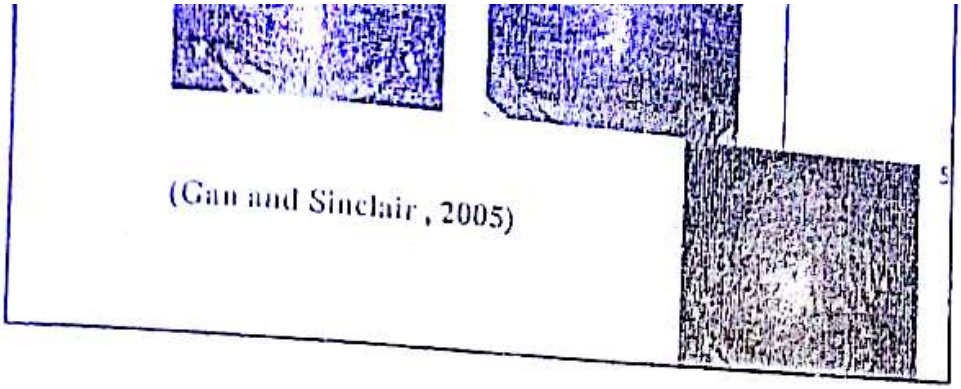


(Gan and Sinclair , 2005)

- Genetic factors predispose to the development of AGA.
- A possible role for Androgen receptor and aromatase genes polymorphisms for development of AGA in men and women were suggested.

4

10

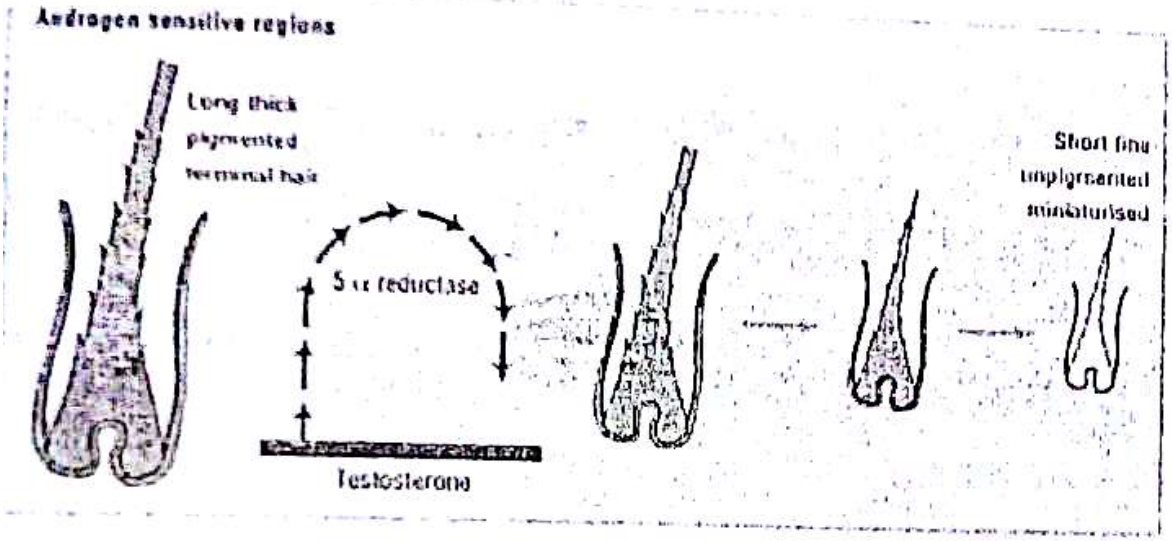
Role of androgen & genetic factors

- Eunuchs do not go bald (Hippocrates).
- Men castrated before puberty do not go bald, latter in life halt the progression of hair loss.
- Male pattern hair loss may be noted in men treated with testosterone.

- Loss of hair in AGA is due to gradual reduction

- Male pattern hair loss may be noted in men treated with testosterone.

- Loss of hair in AGA is due to gradual reduction in the duration of anagen, prolongation of the latent period of the hair cycle and miniat. of terminal hair follicles.
- Affects 50% of men by 50 years of age.
- Nearly 50% of women.



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Minoxidil

- In 1970, was first used as oral medication for Hpt.
- Serves as arteriolar vasodilator.
- Specifically open K channels.
- Hypertrichosis was found as side effect (24 -100%).
- Observed more in women and at lower doses.

- No endocrinal abnormalities.
- Long term oral use → darkening of the skin & coarsening of facial features.
- In 1979, hypertricosis was reported in dermatology literature.

Mechanism of action

1. Vasodilatory effect (K channel opener).

– Laser Doppler velocimetry.

4

1- VD

1- VD

2- angiogenesis

3- slow senescence of keratin

4- antiapoptic

5- enhance cell prolif.

6- immunoregulatory T cells

3. Slows the senescence of keratinocytes (Action on EGF).

4. Antiapoptotic effect (Action on Bcl_2).

5. May enhance cell proliferation (DNA synthesis).

5

- Zapacosta (1980) noted reversal of AGA in a patient on oral minoxidil
- Limitations to use oral form due to side effects.
- In 1984 topical Minx. was used for ttt of AGA.
- 5% solution was better in achieving hair growth.

3

7- ↓ collagen Synthesis
antiandrogen.

2. Angiogensis through upreg. of the expression of

7- ↓ collagen Synthesis
anti androgen.

- Angiogensis through upreg. of the expression of VEGF mRNA in hair papilla cells.
  - Minoxidil $\xrightarrow{\text{sulfotransferase}}$ Min. sulphate → stimulate hair follicles.
  - Lower outer root sheath is the most likely site of conversion.
  - Individual variations (scalp level).
  - Individuals with greater level → better response.

5

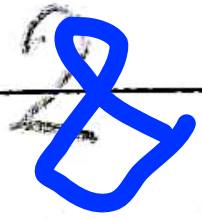
7. Immunoregulatory role in the hair follicles (suppressive effect on T-lymphocytes).
   - This may explain its role in AA.
8. Antiandrogen effects.
9. Suppression of collagen synthesis.

7

Efficacy & safety:

- Often rely on subjective assessments by patient or investigator.

- Objective measures like hair count & hair weight.



Timeline for FDA approval of Minoxidil

- 1970 – [illegible] the FDA for severe hypertension
- 1988 – FDA [illegible] 2% solution, with prescription for hair loss [illegible] FDA
- 1992 – FDA approval for the 2% solution for hair loss in women

- 1996 – FDA approval for the 2% solution for (use in men and women with AGA.
- 1997 – FDA approval for the 5% solution for use in men, labeled as "extra strength for men".
- 2006 – FDA approval for the 5% foam for OTC men.

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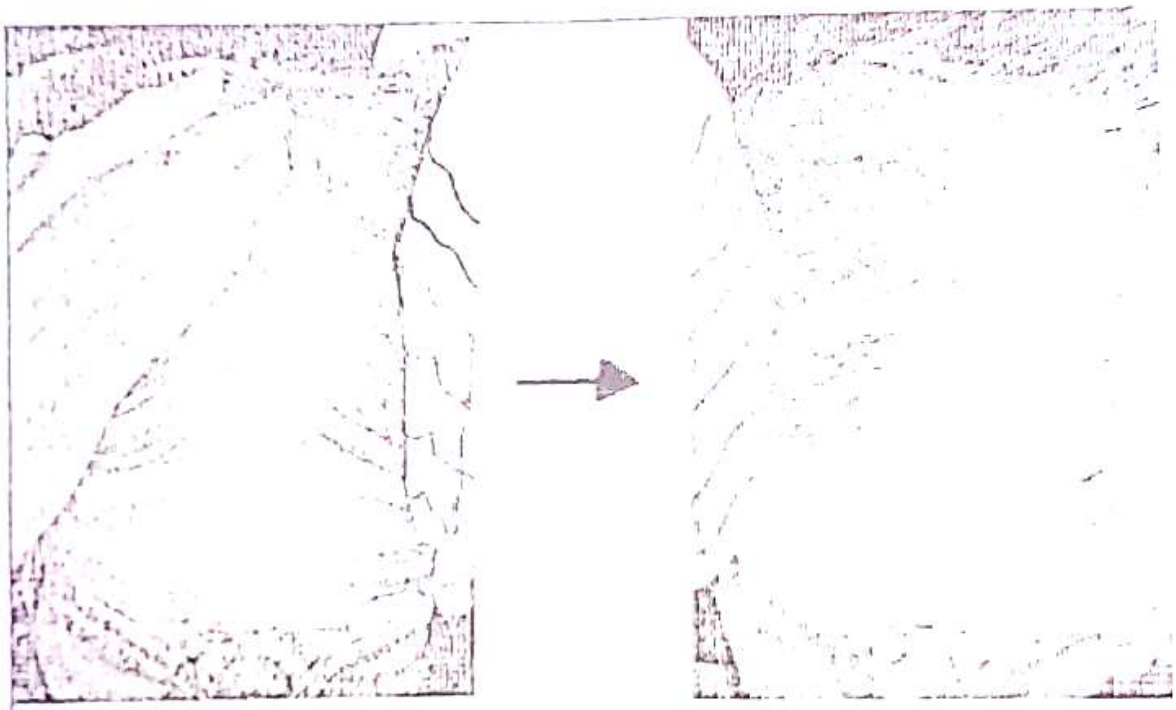

Female-Pattern Hair Loss before and after [illegible]
[illegible] Minoxidil

13

in prostate cancer
PSA increased

في البنات اللي بها خودا
Mask بيقل بيجيل ← finasteride
على الوش

Androgenetic alopecia

Early studies testing low (2 – 3%) strength.

A 5 – year follow up for 31 men (price et al, 1999).

- Hair regrowth tended to peak at one year.
- Significant increase in hair weight.

Greater hair growth can be achieved with 5% solution.

Pruritus, irritation, and hypertrichosis occur more with 5% solution.

Cancer

used

12/20/2015

2

- Randomized, placebo controlled trial:
  - In men: demonstrated 45% more hair growth at week 48 in the 5% (Olsen et al, 2002)
  - In women: demonstrated significant increased hair growth in both 5% & 2% group over the placebo (Lucky et al, 2004)
- Recently, minoxidil was developed into a 5% foam formula.

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Alopecia areata

- Minoxidil was first testing for tt of AA.
- Its efficacy was not sufficient for approval by FDA.

- Recently, minoxidil was developed into a 5% topical formula.

6

Alopecia areata

- Minoxidil was first testing for ttt of AA.
- Its efficacy was not sufficient for approval by FDA.
- AA respond better than A. totalis or universalis.
- Best response rate 80%.
- The effect is due to immunosuppressive effect.
- Histologically demonstrate decreased perifollicular infiltrate.

14

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   - This may explain its role in AA.
8. Antiandrogen effect.
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- 1979 – Oral formulation approved by the FDA for severe hypertension.